QUALITY BY DESIGN APPROACH TO THE STABILITY INDICATING METHOD DEVELOPMENT AND VALIDATION FOR SOME DRUGS AND ITS FORMULATION

A

SYNOPSIS

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1. INTRODUCTION:

Recently the concept of "Quality by Design" (QbD) gaining much attention among pharmaceutical industries for maintaining Quality. It serves as a bridge between industry and drug regulatory authorities to move towards a scientific, risk based, holistic and proactive approach for development of pharmaceutical product. It mainly covers designing and developing formulations and manufacturing processes to ensure predefined product quality [1].

Some of the QbD elements include defining target product quality profile, designing product and manufacturing processes, identifying critical quality attributes, process parameters, and sources of variability & controlling manufacturing processes to produce consistent quality over time The purpose of this article is to discuss the concept of pharmaceutical Quality by Design and describe how it can be help to ensure pharmaceutical quality & drug development [1].

Pharmaceutical industry is constantly searching the ways to ensure and enhance product safety, quality and efficacy. However, drug recalls, manufacturing failure cost, scale up issues and regulatory burden in recent past produce huge challenge for industry. In traditional, the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on implementing quality by design (QbD), a science-based approach that improves process understanding by reducing process variation and the enabling process-control strategies [1].

Instead of relying on finished product testing alone, QbD provides insights upstream throughout the development process. As a result, a quality issue can be efficiently analyzed and its root cause quickly identified. QbD requires identification of all critical formulation attributes and process parameters as well as determining the extent to which any variation can impact the quality of the finished product [1-2].

1.1 Key characteristics of QbD [6]

- A tool for focused & efficient drug development
- Dynamic and systematic process
- Relies on the concept that Quality can be built in as a continuum
- It is applicable to Drug Product and Drug Substance development (chemicals / biologics)
- It is applicable to analytical methods
- Can implemented partially or totally
- Can be used at any time in the life cycle of the Drug
- Always encouraged by Regulators.

1.2 Benefits of QbD [1]

- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Empowerment of technical staff
- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management
- Reduce end-product testing
- Speed-up release decision

QbD is defined in ICH guidelines Q8(R2) as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" ICH guidelines suggest quality in the design to eliminate risk or failures of the process and thus the product. In this approach, the quality associated process variables are defined, their interactions studied, control strategy implemented, and finally, the method is continually monitored [10].

The analytical method development for a drug is also a process, and quality principles in the ICH guidelines can be implemented in the design of the method development.

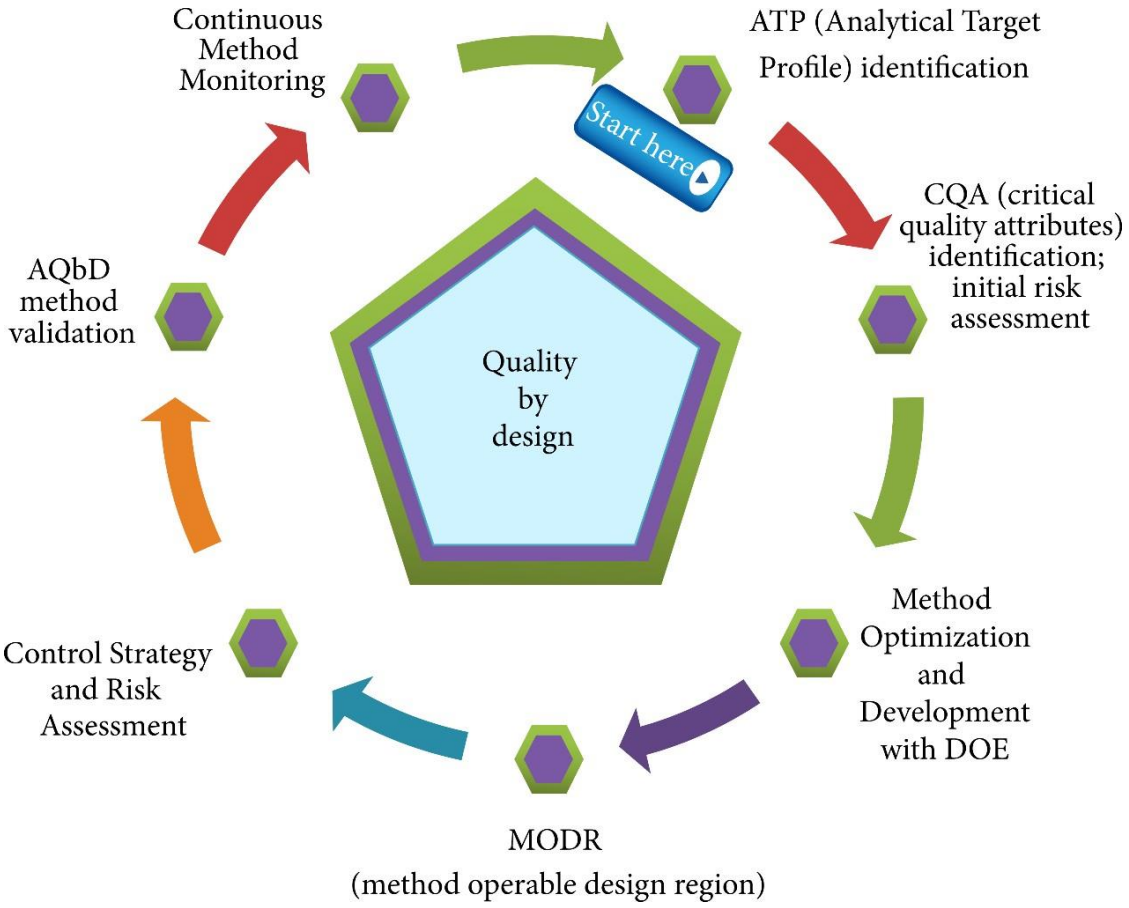
Continuous Method Monitoring
ATP (Analytical Target Profile) identification
Start here
CQA (critical quality attributes) identification; initial risk assessment
AQbD method validation
Quality by design
Method Optimization and Development with DOE
Control Strategy and Risk Assessment
MODR
(method operable design region)

Figure 1: A QbD tools and life cycle.

1.3 Steps involved in analytical development by QbD approach[10]

- ATP (Analytical Target Profile) identification
- CQA identification, Initial Risk Assessment
- Method Optimization and development with DOE
- MODR (Method Operable Design Region
- Control Strategy with Risk assessment
- A QbD Method Validation
- Continuous Method Monitoring

2. RATIONALE OF RESARCH WORK

- we have decided to work on the QbD approach to the stability indicating method development and validation for some drugs and its formulation.
- Pharmaceutical industry has focused on product Quality, Safety, and Efficacy. Product quality has been increasing by implementing scientific tools such as QbD (Quality by Design) and PAT (Process Analytical Technology). Scientific approaches will provide the clear and sufficient knowledge from product development to manufacturing.
- These QbD tools will minimize the risk by increasing the productivity and quality. Nowadays QbD approach has been successfully implemented in generic formulation development.
- Present study will indicate the importance of QbD approach in method development and validation of the pharmaceutical product which increase quality of medicine.
- The stability testing is to provide evidence on how the quality of drug substance varies with time under the influence of variety of environmental and stress factor which increase robustness of the method.

3. REVIEW OF LITRATURE

Venu kamani *et al.*, [11] (2021) had reported a significant official of HPLC method thatresolve the impurities and degradation product generated during stability studies. Therefore, an isocratic RP-HPLC-UV method was developed for the determination of Dacomitinib in the presence of its related impurities and degradation products. The separation of Dacomitinib, impurity 1 and 2 was achieved on Agilent ZORBAX Eclipse (250×4.6 mm; 5 µ id) column as stationary phase, 0.1M sodium perchlorate at pH 5.6, acetonitrile as mobile phase in the ratio of 20:80 (V/V) at a flow rate of 1.0 mL/min in isocratic condition as mobile phase and UV detection was carried at 253 nm. In the optimised conditions, well resolved and retained peaks were observed at a retention time of 5.8 min, 4.0 min and 7.7 min for Dacomitinib, impurity 1 and 2 respectively. In the developed method, a very sensitive detection limit of 0.06 and 0.025 µg/mL was observed for impunity 1 and 2 respectively.

Kirti kumari *et al.*,[12] (2021) had reported a simple, sensitive and specific HPLC method is developed and validated to quantitatively estimate dacomitinib in the pharmaceutical's dosage form. Chromatographic separation was performed on an Kromasil C18 Column (250 x 4.6 mm; 5µm) via isocratic elution with mobile phase consisting of 0.2% triethylamine solution (pH = 3.0 adjusted with 85% orthophosphoric acid): acetonitrile (70:30) with a flow rate of 1mL/min. The detection was achieved with UV/Vis detector with a detection wavelength of 260 nm. The method was validated in terms of linearity, sensitivity, precision, accuracy and limit of quantification tests. Dacomitinib can be successfully separated with good linearity (the regression equation is A =7566.3C + 1610.0; R2 = 1.0) and perfect recovery with the results of accuracy were in the range 98-102%.

Khushbu Patel *et al.*, [13] (2022) had reported a A new simple stability indicating reverse phase liquid chromatography method was developed by employing Quality by Design (QbD) approach for the simultaneous determination of Linagliptin and Metformin HCl. Within QbD Centre composite design (CCD) in order to achieve a good separation and resolution. The developed method is effective to separate Linagliptin and Metformin HCl with a good chromatographic resolution of 6.4. Chromatographic separation was acquired with column Water C_{18} (250mm x 4.5mm x

5µm) at flow rate 1.0 ml/min with the mobile phase consists of acetonitrile and methanol (75:25 % v/v). The detection of Linagliptin and Metformin HCl was carried out at 245nm. The proposed method was validated according to ICH guidelines. The method was linear in range of 0.5-3µg/ml and 100-600µg/ml of Linagliptin and Metformin HCl respectively and recovery were in the range of 98% to 102%. The degradation product found in stress patterns were well separated among the drug compounds. The method was validated to be specific, rapid, precise and robust for routine analysis in its pharmaceutical dosage form.

Syed Salman Lateef *et al.*,[14] (2014) had reported A quality-by-design (QbD) approach to method development can potentially lead to a more robust/rugged method due to the emphasis on risk management. This study applied a QbD approach to linagliptin stability indicating method development using Fusion AE automated QbD method development software (S-Matrix) and an Agilent 1200 Infinity Series Method Development Solution. The allowed deviations of the method variables are determined within the design space – the Proven Acceptable Ranges (PARs). The critical method variables in a linagliptin stability-indicating method are percent organic 90.5 ± 1.5 and pH 7.7 ± 0.1 at a column temperature of 45 °C. The potential interference of method variables in terms of desirable method responses was determined, leading to a better understanding of the method, and achieving desirable method quality.

Arijit Gandhi *et al.*,[15] (2016) had reported the concept of "Quality by Design" (QbD) gaining much attention among pharmaceutical industries for maintaining Quality. It serves as a bridge between industry and drug regulatory authorities to move towards ascientific, risk based, holistic and proactive approach for development of pharmaceutical product. It mainly covers designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include defining target product quality profile, designing product and manufacturing processes, identifying critical quality attributes, process parameters, and sources of variability & controlling manufacturing processes to produce consistent quality over time The purpose of this article is to discuss the concept of pharmaceutical Quality by Design and describe how it can be help to ensure pharmaceutical quality & drug development.

K Ramya sri *et al.*,[16] (2021) had reported the Quality by design (QBD) is a modern approach that began with predefined objects like safety efficacy of the product widely using in the pharmaceutical development. The main aim of QBD in pharmaceutical development is to provide safety, efficacy of the product. QBD focus to impart quality in the design itself. Food and Drug administration introduced QBD to understand the manufacturing process. This paper gives an idea about international council for Harmonization (ICH) guidelines for pharmaceutical development, quality risk management and pharmaceutical quality system, to maintain the quality of the product. A brief discussion on tools used in QBD, regulatory-industry views and scientifically based QBD was given. An emphasis on drug substances, excipients, container closure systems, manufacturing of bio therapeutics with relevant process development was portrayed.

Nirmal M Kasekar *et al.*,[17] (2017) had reported A new simple, accurate, rapid, selective and robust high pressure liquid chromatography (HPLC) method was developed and validated for estimation of itraconazole in bulk and marketed formulation. Acetonitrile and double distilled water was used as a mobile phase for chromatographic separation and estimation on HiQSil C18- HS (250 × 4.6 mm) in the ratio of 90:10 v/v at flow rate of 1.0 ml/min. The detection was carried out with UV detector set at 263 nm. The retention time for itraconazole was found to be 7.75 minutes. The linearity range for itraconazole was found to be 5-60 µg/ml with coefficient of linear regression 0.991. The method was validated in accordance with the requirements of International Conference on Harmonization (ICHQ2 (R1) 2005) guidelines for accuracy, precision, LOD & LOQ, linearity and robustness.

Jyoti Shinde *et al.*,[18] (2022) had reported the present study gives the development of the RP HPLC method by using Quality by Design followed by validation of developed method for estimation co Favipiravir in bulk and tablet dosage form. The central composite method was applied on organic Phase concentration & buffer PH for initial Screening studies. The selection of optimum chromatographic condition was carried out by design space numerical, graphical optimization on retention time, Peak asymmetry & Theoretical Plates. Optimized analytical method consisted Acetonitrile: water (80:20%v/v) as mobile phase, pH 5, flow rate 1ml/min, a wavelength 323 nm.

Favipiravir was eluted with retention time 2.7 min & peak area 51248, Favipiravir showed good linear relationship in range of 10-90 µg/ml with a correlation coefficient of 0.9985. The % RSD for intraday, inter day precision & Repeatability was found to be 0.88, 0.65 & 0.97 respectively. Limit of detection & quantification was found to be 104.44 µg/ml &. 316.5 µg/ml. The method validation parameters were in the prescribed limit as per ICH guidelines.

Krunal Y. Pate *et a.*,[19] (2021) had reported an efficient experimental design based on central composite design of two key components of the RP-HPLC method for ceftriaxone (mobile phase and pH) is presented. The chromatographic conditions were optimized with the Design Expert software 11.0 version, i.e., Phenomenex ODS column C18 (250 mm × 4.6 mm, 5.0 µ), mobile phase used acetonitrile to water (0.01% triethylamine with pH 6.5) (70:30, v/v), and the flow rate was 1 ml/min with retention time 4.15 min. The developed method was found to be linear with r2 = 0.991 for range of 10–200 µg/ml at 270 nm detection wavelength. The system suitability test parameters, tailing factor and theoretical plates, were found to be 1.49 and 5236. The % RSD for intraday and inter day precision was found to be 0.70–0.94 and 0.55– 0.95 respectively. The robustness values were less than 2%. The assay was found to be 99.73 ± 0.61%. The results of chromatographic peak purity indicate the absence of any coeluting peaks with the ceftriaxone sodium peak. The method validation parameters were in the prescribed limit as per ICH guidelines.

S. Sayare *et al.*, [20] (2019) had reported A Simple, efficient and reproducible method for the estimation of Vigabatrin (VGB) from bulk and pharmaceutical formulation has been developed using reversed phase high performance liquid chromatography. The method involves derivatization of the primary amine group of VGB with 9-fluorenylmethyloxycarbonyl chloride (FMOC) followed by isocratic separation using a mobile phase consisting of acetonitrile: water (97.5 : 2.5% V/V). Column used was Finpak SIL C18 (250 X 4.6 mm internal diameter) 5 µ with flow rate of 1 mL/min. The detection wavelength used was 265 nm. The retention time of VGB-FMOC comples was found to be 3.89 min. Linearity of drug was 5-30 µg/mL. The performance of analysis was studied and the validated method showed excellent performance in terms of selectivity, specificity, sensitivity, precision and accuracy. No interferences were found from excipients and other impurities.

4. IMPORTANCE OF THE STUDY

- Quality by design is an approach that aim to ensure the quality of the medicine by employing statistical, analytical and risk-management methodology in design, development and manufacturing of medicine.
- Present study indicates importance of QbD approach in method development and validation of the pharmaceutical product which increase quality of medicine.
- The stability testing is to provide evidence on how the quality of drug substance varies with time under the influence of variety of environmental and stress factor which increase robustness of the method.

5. AIM AND OBJECTIVES

AIM:

- Quality- by-design approach to the stability indicating method development and validation for some drugs and its formulations**.**

OBJECTIVES:

- To develop stability indicating RP-HPLC method for some drugs and its formulation.
- To apply QbD approach using statistical experimental design (DoE) to develop a robust method.
- To validate the developed methods according to ICH Q2(R1) Guidelines for the following parameter:
  - Accuracy
  - Linearity
  - Precision
  - LOD (limit of detection)
  - LOQ (Limit of Quantification)
  - Specificity
  - Robustness
- To carry out forced degradation study on drugs.

6. RESEARCH METHODOLOGY

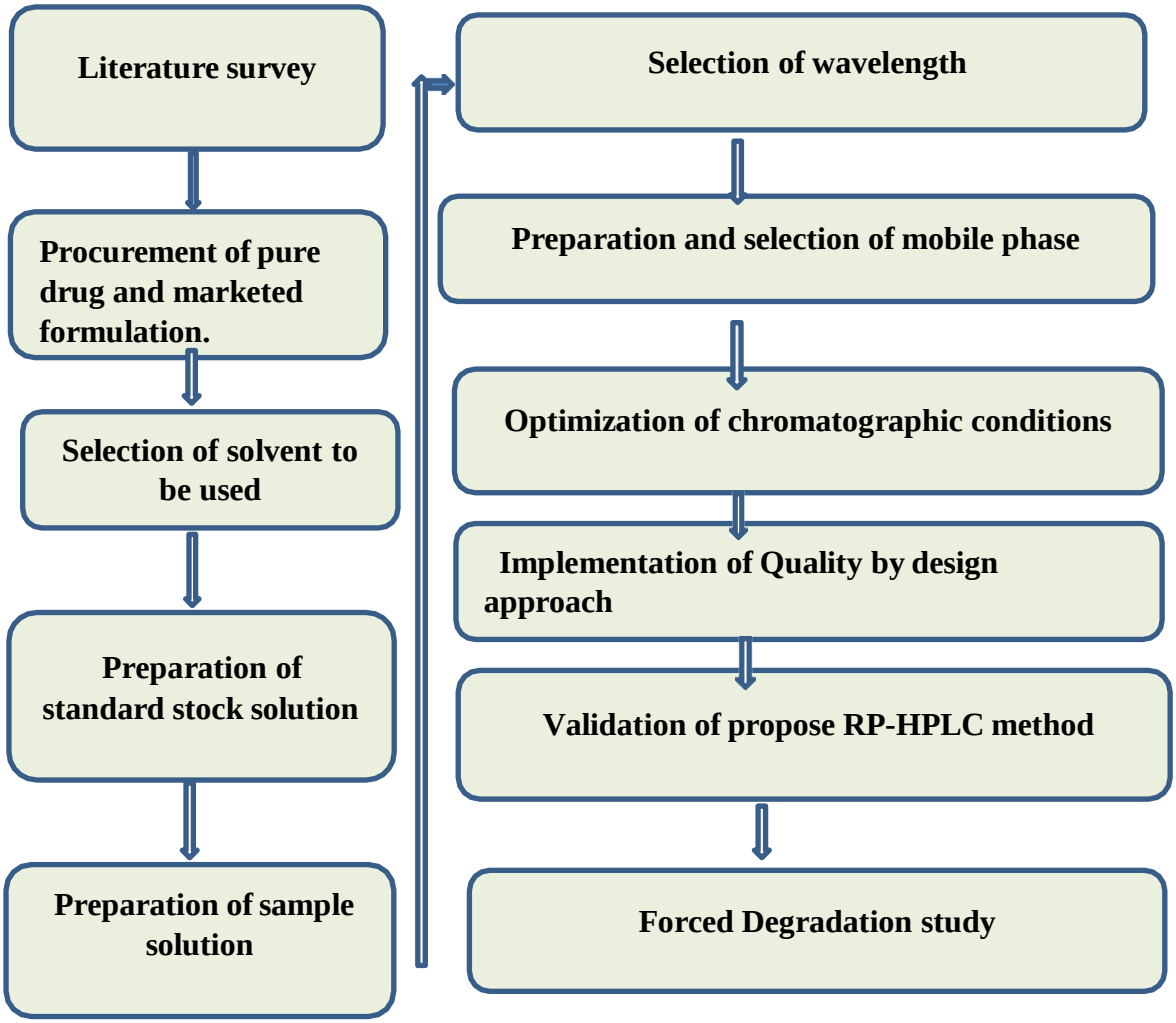
Literature survey
Procurement of pure drug and marketed formulation.
Selection of solvent to be used
Preparation of standard stock solution
Preparation of sample solution
Selection of wavelength
Preparation and selection of mobile phase
Optimization of chromatographic conditions
Implementation of Quality by design approach
Validation of propose RP-HPLC method
Forced Degradation study

Figure 2: Flow chart of research methodology use.

7. RESEARCH WORK PLAN

Sr. No.	Work	Period
1.	Literature survey	6 months
2.	Procurement of API and Excipients	2 months
3.	Selection of solvent to be used	2 months
4.	Preparation of standard stock solution and sample solution	1 months
5.	Selection of wavelength and Preparation and selection of mobile phase	1 months
6.	Optimization of chromatographic conditions	3 months
7.	Implementation of Quality by design approach	6 months
8.	Validation of propose RP-HPLC method	6 months
9.	Forced Degradation study	3 months
10.	Other suggested work and compilation of data	6 months
	Total duration of work	**36 months**

8. OUTCOME OF RESEARCH

- Understanding of QbD approach for analytical method development and also to understand the forced degradation effects on drugs and its formulations.
- Validation of developed method as per ICH Q2(R1) Guidelines.

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